Refer to: Hyde L: Rifampin in the treatment of pulmonary tuberculosis. Calif Med 117:18-21, Dec. 1972

Rifampin in the Treatment of Pulmonary Tuberculosis

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■ *Rifampin is a newer semi-synthetic derivative of rifamycin. Its advantages over other derivatives are good oral absorption, high blood levels, and slower excretion rate.*

Rifampin has been studied in 68 patients and results can be summarized as follows:

- *There has been no evidence of significant toxicity.*
- *In a randomized study of active tuberculosis patients who had not received prior chemotherapy, isoniazid-rifampin and isoniazid-aminosalicylic acid regimens were equally effective.*
- *In retreatment patients with active, positive tuberculosis, the regimen of isoniazid, rifampin, and ethambutol proved to be very effective, especially when the two latter drugs had not been used previously.*
- *In patients with pulmonary infections caused by atypical acid-fast bacilli, results varied with the organism isolated and the extent of disease.*

Rifampin is a potent, relatively non-toxic drug especially useful in the retreatment of pulmonary tuberculosis in patients who have never received this drug previously. There is little justification for its use in initial therapy except in rare cases.

RIFAMPIN IS A NEWER *semi-synthetic* N-methylpiperazine derivative of rifamycin sv, isolated from a strain of Streptomyces mediterranei in 1959 by Sensi and others.[1] More than 400 derivatives have been prepared from rifamycin, and rifampin has been found to be effective against tubercle bacilli and atypical mycobacteria *in vitro*.[2]

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Submitted February 8, 1972.

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Clinical studies with patients having tuberculosis, have indicated significant therapeutic effect, with reports at the 27th Veterans Administration-Armed Forces Pulmonary Disease Research Conference by Gyselen et al[3] and Verbist and Gyselen.[4] The advantages of rifampin over other derivatives of rifamycin sv are good oral absorption, high blood levels, and slower excretion rate.

Rifampin is an orange-red crystalline powder, tasteless, and stable at room temperature. It is readily absorbed from the gastrointestinal tract

and is excreted mainly by the kidney and liver, but also in sputum. The drug is better absorbed on an empty stomach, reaching a peak blood concentration between one and four hours after ingestion of 600 mg, with levels of 7 to 9.5 micrograms per milliliter—greatly in excess of the minimal inhibitory levels required for Mycobacterium tuberculosis.[5]

Methods

Patients with pulmonary disease caused by acid-fast bacilli were studied in four groups. All had evidence of either active pulmonary tuberculosis caused by niacin-positive organisms or of pulmonary disease caused by atypical niacin-negative acid-fast bacilli. Each patient received the examinations noted in Table 1. The items in Group B and D were first repeated weekly. With the absence of toxicity, they were repeated biweekly, and then subsequently monthly. Audiometric and ophthalmologic examinations were repeated monthly.

Dosage of drugs used was: isoniazid (INH) 300 mg once daily by mouth; aminosalicylic acid (PAS) 4 grams three times a day by mouth; streptomycin (SM) in variable dosage, but usually 1 gram daily intramuscularly for the first month, 1 gram three times weekly for the next month, and then 1 gram twice weekly for an additional month; ethambutol (EMB) 15 mg per kilogram of body weight, once daily by mouth; rifampin (RFP) 600 mg once daily by mouth, before breakfast.

Results

Data were analyzed in four groups:

A. *Toxicity*

Of the 68 patients receiving rifampin for variable lengths of time, only minor changes in the serum glutamic-oxalacetic-transaminase (SGOT) were noted in 10 percent of the patients. Using the Sequential Multiple Analyzer (Technicon), normal values for SGOT are up to 50 milliunits per ml. Seven patients had increases in SGOT, up to 100 milliunits per ml in three cases. Elevations persisted from one to three months. These figures do not differ from those for patients with tuberculosis receiving isoniazid-para-aminosalicylic acid (INH-PAS) regimens, and from non-tuberculous emphysema patients not receiving any anti-tuberculosis drugs. No other drug reactions were noted and therapy was not stopped because of toxicity in any patient.

TABLE 1.—*Examinations Performed Regarding Potential Toxicity*

A.	History and physical examination
B.	Complete blood count
	Hematocrit
	Sedimentation rate
	Platelet count
	Routine urinalysis
C.	Audiometric examination
	Ophthalmologic examination
D.	Serum chlorides
	carbon dioxide
	potassium
	sodium
	urea nitrogen
	glucose
	calcium
	phosphorus
	uric acid
	cholesterol
	total protein
	albumin
	total bilirubin
	alkaline phosphatase
	lactic dehydrogenase (SLDH)
	glutamic-oxalacetic-transaminase (SGOT)

B. *Initial Therapy of Patients with Active Pulmonary Tuberculosis.*

Fifty patients with niacin-positive tubercle bacilli in the sputum and no previous drug therapy were randomized between INH-RFP and INH-PAS. Ninety-two percent of the patients had sputum conversion after 16 weeks of therapy on either regimen. The median time for sputum conversion to occur with both regimens was one and one-half months. Duration of RFP usage varied from three to five months. RFP was discontinued after sputum conversion and before discharge from the hospital, and replaced by a standard anti-tuberculosis drug, usually PAS or EMB. Follow-up of these patients has been relatively brief and no comments are warranted concerning relapse rates.

C. *Retreatment Patients.*

Twenty-five patients with active pulmonary tuberculosis and positive sputum cultures with a history of previous treatment were placed on a regimen of isoniazid-ethambutol-rifampin (INH-EMB-REP). Good results were secured, with 92 percent conversion rates after 16 weeks of therapy. This group included four patients who

had had positive sputum cultures for tubercle bacilli intermittently for 18, 10, and 6 years, and one patient positive consistently for the previous 5 years, but it must be emphasized that none of these patients had received ethambutol or rifampin previously.

D. *Atypical Acid-Fast Infections*

1. *M. kansasii*

Because of the small number of patients, these cases were not randomized. Twelve patients did well on the INH-RFP regimen, as had 20 patients previously treated with various combinations of INH-PAS, INH-SM, INH-SM-EMB. In this small group, sputum conversion occurred in all of the patients.

2. *M. intracellulare (Battey)*

Only six patients were treated with INH-RFP-EMB. If the sputum concentrates were negative and only the cultures positive, results were good (two patients). Patients with extensive bilateral disease and positive sputum concentrates for acid-fast bacilli usually did poorly on the INH-RFP-EMB regimen, as they usually did with other regimens. Patients with Battey infections often require five or six drug regimens.

The above results in all of the groups must be considered preliminary in view of the relatively short period of follow-up observations (months rather than years).

Discussion

Nitti reported the use of rifampin alone with 49 patients having positive sputum, and indicated that this drug had antituberculosis activity equivalent to isoniazid, that rifampin was well tolerated and apparently non-toxic, but that rifampin used alone permitted development of bacterial resistance.[6]

A Belgian cooperative study involving 120 patients with advanced pulmonary tuberculosis and positive sputum concentrates for acid-fast bacilli, compared four regimens: rifampin-placebo, rifampin-isoniazid, rifampin-ethambutol, and isoniazid-ethambutol. The rifampin-isoniazid treatment yielded 100 percent sputum conversion with negative cultures after completion of 13 weeks of treatment, and was slightly more effective than the three other regimens. No toxicity to rifampin was noted.[7]

Raleigh has coordinated two Veterans Administration Cooperative Studies—one for retreatment patients with active tuberculosis using rifampin and ethambutol,[8] and the other involving patients with advanced, previously untreated pulmonary tuberculosis. In the latter study, three regimens were compared: isoniazid-streptomycin, isoniazid-rifampin, and streptomycin-rifampin. Preliminary observations indicate these to be equally effective with about 93 percent conversion rates after 26 weeks of therapy.

The Veterans Administration studies confirmed "that rifampin is a drug of very low toxicity and apparently of high efficiency."[9] At recent meetings of the American Thoracic Society, Raleigh and Lester each described his experience with patients requiring retreatment for far advanced active pulmonary tuberculosis.[10,11] In the Veterans Administration Rifampin Retreatment Study, Raleigh[12] reported that sputum conversion occurred in 94 percent of 48 patients. Unfortunately, 20 percent of these patients relapsed within several months. Various clinical trials indicate that rifampin is an effective, virtually non-toxic drug useful in the treatment of tuberculosis, but its exact role is far from clear.

Indiscriminate use of rifampin in initial therapy will decrease greatly its usefulness, if retreatment or additional treatment is required later. In Great Britain, it is felt that there is little justification for use of rifampin in initial treatment except in rare cases of intolerance to other drugs,[13] and with this I fully agree. Although no significant toxicity was detected in this small group of patients, and in other series of cases, reports of occasional toxicity are well-documented, including hypersensitivity,[7] fatty liver,[10] hepatotoxicity,[11] and thrombocytopenia purpura.[11] An article in *Lancet* in 1969 noted: "More than a hundred reports have been published on the use of rifampicin [rifampin] in man. From all this evidence it can be accepted that the drug is remarkably free from toxicity. As it has mostly been given with other antituberculosis agents, side-effects due to rifampicin cannot with certainty be separated from those due to other drugs."[14] An important disadvantage of RFP is its cost. The daily hospital cost (for 600 mg) per patient is $1.84, compared with daily costs of 0.4 of one cent for INH, 7 cents for PAS, and 27 to 36 cents for EMB. A 1 gram dose of streptomycin costs 10 cents.

The current Veterans Administration Cooperative Study No. 33 randomizes initial therapy pa-

tients with active pulmonary tuberculosis to one of four regimens: INH-EMB, INH-RFP, RFP-EMB, and INH-RFP-EMB. To date more than 300 patients have been randomized. When completed in a few years, this well-controlled, carefully designed study should provide definitive answers to various questions about rifampin.

Present evidence suggests that rifampin is an effective, virtually non-toxic antituberculosis drug, which may be useful in the retreatment of patients with tuberculosis, but it is not indicated for initial therapy.

Grateful acknowledgment is made to Dow Chemical Company for supplies of rifampin used in this study.

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TREATMENT OF THE OBESE LATENT DIABETIC

Obesity is closely associated with latent diabetes as well as diabetes. About seven out of eight diabetics when discovered are overweight. By inference then many overweight people must have latent diabetes. . . . To document this condition, the first thing to do is run an oral glucose tolerance test. You'll find it to be slightly elevated in the obese patient, but at the same time you'll find the insulin levels to be inordinately high. . . .

The question comes up "How would you treat this latent diabetes?" You treat it first by weight reduction which, as all of you know, is almost impossible to achieve over a long period of time. In the literature, it's cited that 5 percent of weight reduction is permanently successful and no more.

If that doesn't work, what do you use to improve carbohydrate tolerance? The logical thing is phenformin (DBI) rather than the sulfonylureas because you already have a lot of insulin. What you want to do is facilitate the utilization of glucose which you can do almost independently of insulin with DBI whereas the sulfonylureas push out more insulin. So you give DBI. You find the insulin levels definitely do go down, and yet the carbohydrate utilization improves. So on theoretical grounds, DBI is the method of choice for oral therapy in obese patients. This does not mean that if you use sulfonylureas you can't regularize the blood sugar levels and at the same time achieve a weight reduction, but theoretically DBI is better.

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Extracted from *Audio-Digest Internal Medicine*, Vol. 17, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057